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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/966,233	11/07/97	LEE S	241800

HM22/1003

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EXAMINER	
ALLEN, M	
ART UNIT	**PAPER NUMBER**
1631	57

DATE MAILED: 10/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/966,233	Lee
Examiner	**Group Art Unit**
Marianne P. Allen	1631

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *3, 11-15, and 24-31* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *3, 11-15, and 24-31* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1630, Art Unit 1631.

PROSECUTION IS HEREBY REOPENED in view of the interim guidelines on utility and written description published subsequent to the final rejection. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(a) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(b) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant points to basis for the claimed subject matter on pages 9-10 of the specification. The specification at these pages does not appear to disclose the hybridization conditions recited in the claim with respect to Figures 11A and 11B. Only Figure 2 is mentioned. Applicant is requested to point to specific basis (page and line number) for the claim limitations. Should this rejection be overcome, this claim would be subject to the enablement rejection set forth below. Applicant's arguments with respect to Figures 11A and 11B are not persuasive. The specification does not link the particularly claimed hybridization conditions to those sequences present in these Figures.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Definitions: [from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

> "Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or

diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are

"throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. § 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP at §§ 2107 - 2107.02.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 11-15, 22, and 24-31 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by either specific and/or substantial utility or a well established utility.

Claims 3, 22, and 24-25 are directed to isolated DNA segments encoding GDF-1 proteins. Claim 31 is directed to a complementary DNA segment. Claims 11 and 26 are directed to vector containing a DNA segment encoding GDF-1. Claims 12-14 and 27-29 are directed to host cells.

Claims 15 and 30 are directed to methods of producing recombinant GDF-1. The protein products lack patentable utility for the reasons set forth below; therefore, the methods of producing the protein and vectors and hosts used therefore (claims 11-15 and 26-30) to make these protein products must also lack patentable utility.

The specification discloses the use of the DNA sequences, vectors, and host cells to make the encoded protein. This is not a specific asserted utility because it is generally applicable to any encoding DNA sequence.

The specification discloses using the GDF-1 proteins to make antibodies. This is not a specific asserted utility because it is generally applicable to any protein.

Example 4 of the specification concerns the expression pattern of GDF-1 using the nucleic acids in Northern blot analysis. Contrary to applicant's assertions, the specification does not disclose a use of the DNA segments or proteins as a lineage marker here or on page 12, lines 20-23. It is noted that even if the specification explicitly set forth such a use, this would not be a specific asserted utility because it too is generally applicable to any DNA segment or protein. Likewise, use as a temporal and/or tissue-specific marker is not explicitly set forth in the specification and it is not considered to be a specific asserted utility because it too is generally applicable to any DNA segment.

The specification discloses that the GDF-1 proteins **may** have any of a number of biological activities based upon similarity to members of the TFG-β superfamily. It is noted that these activities vary quite widely. The similarities between particular GDF-1 proteins and the

TGF-β family members range from 26-52% on the amino acid level. (See specification page 12, lines 8-20.) As the specification fails to point to identify a particular activity associated with GDF-1 proteins, these are not considered to be specifically asserted utilities either.

Furthermore, applicant is reminded that even a single amino acid change or mutation can alter the function of a protein in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed protein and the indicated similar proteins of known function and therefore lacks support regarding utility and/or enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al.[BioEssays, Volume 18, Number 12, pages 973-981[1996)]; Wells et al.[Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; and Russell et al.[Journal of Molecular Biology, Volume 244, pages 332-350 (1994)].

The specification states on page 12 that a potential use for GDF-1 is as a diagnostic tool as a specific marker for the presence of tumors arising from cell types that normally express GDF-1. Other uses are as an indicator for developmental anomalies in prenatal screens for birth defects or genetic diseases. These are not considered to be specific as the specification does not associate

any particular tumor, birth defect, or genetic disease with GDF-1 proteins or the DNA segments that encode them. The examiner notes that none appear to be associated with this protein even now, well after the effective filing date.

Nor do these uses satisfy the requirement of a substantial utility.

The claimed GDF-1 proteins are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. The specification makes clear that further experimentation is necessary to confirm the activity and uses of the protein. The need for such research clearly indicates that the protein and/or its function is not disclosed as to a currently available or substantial utility.

Applicant appears to be relying upon the statement in the specification at page 14, lines 2-8, that "if GDF-1 possesses a similar activity, as is indicated by its specific expression in the central nervous system...GDF-1 will likely prove useful in vitro for maintaining neuronal cultures..." This passage refers to the known protein activin. Note that this is one of many uses disclosed predicated upon further experimentation to characterize the protein. Again, identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use.

Applicant has previously submitted the Ebendal declaration under 37 CFR 1.132. The stated reasons for this submission vary and presently applicant states that the declaration was submitted to rebut the examiner's conclusion that GDF-1 activity could not be predicted. Whatever the reasons for the submission, the declaration supports the examiner's position that

GDF-1 activity at the time of the invention was not known, could not have been predicted, and that there was no specific or substantial utility set forth as evidenced by the degree of experimentation conducted to find an activity.

The Ebendal declaration sets forth that recombinant human GDF-1 (amino acids 255-373 fused to 34 additional amino acids) was produced in E. coli and recovered as a dimer. This product potentiates human NT-3 fibre outgrowth. The assays used to establish this biological activity are referenced to Ebendal (1995) and Ernfors (1990). The declaration asserts that this biological activity on neurons is similar to other members of the TGF-β superfamily.

First of all, the particular material tested is not disclosed in the specification. That is, while Figure 11B discloses the human GDF-1 sequence, the portion of this protein and the particular fusion partner used in the declaration experiments do not appear to be disclosed in the specification. Use of the particular pRSET vector by Invitrogen does not appear to be disclosed in the specification. Use of a dimer versus a monomer does not appear to be disclosed in the specification. The fibre outgrowth assay of Ebendal et al. (1995) was developed after the effective filing date of the application. The Ernfors et al. (1990) reference is also post-filing date for the ultimate parent application. Furthermore, it discloses fibre outgrowth activity of NT-3 (although not named as such in this reference) but does not disclose similar activity of TGF-β superfamily members or GDF-1 proteins. It is noted that the declaration evidence indicates that GDF-1 alone was ineffective to evoke fibre outgrowth.

It appears that the potentiating activity between the TGF-β superfamily member OP-1 and NT-3 was not known until well after the effective filing date. (See Bengtsson et al., Journal of Neuroscience Research, 1998.) It is noted that the receptors discussed were not known at the time of the invention nor does the reference generally postulate this activity to all other members of the superfamily. The involvement of the GDF family was only determined well after the effective filing date. (See Ebendal et al., Journal of Neuroscience Research, 1998.) It was not discovered until well after the effective filing date that TGF-β3 potentiates the survival achieved with NT-3 and NT-4. (See Krieglstein et al., Neurochemical Research, 1996.)

Massague provides a review of the TGF-β superfamily at approximately the time of the invention. The reference sets forth the diverse effects of the various members of the superfamily. The potentiating effect of the Ebendal declaration is not disclosed.

In conclusion, the examiner again points applicant to what is stated on page 14, lines 29-33, of the specification. "A determination of the specific clinical settings in which GDF-1 will be used as a diagnostic or as a therapeutic tool await further characterization of the expression patterns and biological properties of GDF-1 both under normal physiological conditions and during disease states."

Claims 3, 11-15, 22, and 24-31 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Claims 3, 11-15, 22, and 24-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 3 is directed to DNA segments encoding mouse or human GDF-1. Claim 22 is directed to mammalian GDF-1 proteins defined in an open reading frame of Figure 2 or Figure 11A or Figure 11B. Claims 24-25 specifically include sequence outside the open reading frame. Claim 31 is directed to a complementary sequence under certain hybridization conditions. All of the claims use open language.

First of all, the claim language used clearly encompasses the genomic sequences (particularly apparent in claims 24-25 and 31) which have not been disclosed and are thus not described. It is noted that the sequences disclosed were derived from cDNA sequences. With respect to claim 31, it is particularly noted that the Southern blot experiments in Example 5 demonstrate that even under high stringency hybridization conditions, additional bands were detected in addition to a predominant band and their sequence structure is not described. The specification clearly distinguishes them from partial digestion products.

In addition, the specification provides the sequences of mouse and human GDF-1. The specification further indicates that they have less conservation across species (69%) than other members of the TGF-β superfamily. (See page 31.) The specification contains no disclosure of the expected structure for other members of this family or what structural features identify a

protein as a GDF-1 protein. Furthermore, as the activity of GDF-1 was not known at the time of the invention, the specification does not enable any assays for identification of GDF-1. As such, none of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the GDF-1 [redacted] sequences disclosed in Figure 2, 11A, or 11B, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The DNA itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only the GDF-1 [redacted] sequences disclosed in Figure 2, 11A, or 11B, but not the full breadth of the claim meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
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Therefore, only the GDF-1 protein sequences disclosed in Figure 2, 11A, or 11B, but not the full breadth of the claim meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the

genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant argues that the mouse and human and unsequenced hamster sequences are representative of the genus. This is not agreed with for the reasons set forth above. Applicant further argues that other members can be identified by related hybridization methods and comparison to known members. This is completely contrary to the case law cited. The examiner maintains that the specification and claims lacks structural and functional limitations defining the GDF-1 family of DNA segments and proteins and thus fails to adequately support the genus claimed, particularly as the claims encompass genomic sequences.

Applicant's comments regarding U.S. Patent Nos. 6,008,017 and 6,074,841 are not germane. The specification, prosecution history, and allowed claims have no bearing on this application. Each application is examined independently and on its own merits.

It is believed that all pertinent arguments set forth in the appeal brief filed 7/3/00 have been addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen, whose telephone number is (703) 308-0666. The examiner can normally be reached on Monday-Friday from 9:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028. Official FAX communications may be directed to either (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER
~~GROUP 1800~~
1631